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Siiki, Antti

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A pilot study of endoscopically inserted biodegradable biliary stents in the treatment of benign biliary strictures and cystic duct leaks

Antti Siiki, MD, PhD,¹ Irina Rinta-Kiikka, MD, PhD,² Juhani Sand, MD, PhD,^{3,4}
Johanna Laukkarinen, MD, PhD^{1,4}

Tampere, Lahti, Finland

Background and Aims: Self-expanding biodegradable biliary stents (BDBSs) have recently become available for use in endoscopic retrograde cholangiography (ERC). The aim was to evaluate the effectiveness and safety of novel BDBSs in iatrogenic cystic duct leaks and benign biliary strictures (BBSs).

Methods: Patients providing informed consent were recruited for the prospective study. Braided self-expanding poly-dioxanone BDBSs were inserted using ERC during from 2014 to 2016. Repeated liver function tests and magnetic resonance imaging were performed during follow-up. The main outcomes were treatment success and adverse events.

Results: Thirteen patients, 5 women, median age 67 years (range, 43-79) underwent BDBS insertion for iatrogenic cystic duct leak (n = 7) or BBS (n = 6). Stent insertion using ERC was successful in all cases. All bile leaks were treated uneventfully with BDBSs. In BBSs, the clinical success rate of BDBS therapy was 83% in a median of 21 months of follow-up (range, 14-25). Early ERC-related adverse events included 1 cholangitis (8%) and 1 pancreatitis (8%), both in the stricture group. During the first 90 days, 23% of patients were readmitted for mild cholangitis.

Conclusions: The short- and long-term safety of endoscopically inserted poly-dioxanone BDBSs was satisfactory. The management of cystic duct leaks and benign distal common bile duct strictures was highly successful. Episodes of mild cholangitis during stent indwelling seemed to be typical of BDBSs. The advantage of BDBSs is the avoidance of repeated endoscopy for stent removal. (Clinical trial registration number: NCT02353286.)

An endoscopic insertion device for biodegradable biliary stents (BDBSs) compatible with standard duodenoscopes has become available only recently (Fig. 1). BDBSs could potentially achieve a patency and radial expansion force resembling widely used fully covered self-expanding metal stents (FCSEMSs) while saving the cost and burden of repeated endoscopy for stent removal.¹ The most common biodegradable material for stent manufacturing is currently synthetic polymer poly-dioxanone (Fig. 2); its biocompatibility in human biliary environment is well

established.² Very similar material has been used in absorbable polydioxanone sutures in surgery since the 1980s.³

The widest experience of clinical use of poly-dioxanone BDBSs is from about 100 patients treated percutaneously for refractory biliary strictures. In this study by Mauri et al,⁴ the usefulness and safety of BDBSs were demonstrated in a nearly 2-year follow-up with a stricture resolution rate of over 80%. The case reports of these stents in endoscopic retrograde cholangiography (ERC)

Abbreviations: BBS, benign biliary stricture; BDBS, biodegradable biliary stent; ERC, endoscopic retrograde cholangiography; FCSEMS, fully covered self-expanding metal stent; MRI, magnetic resonance imaging.

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Current affiliations: Department of Gastroenterology and Alimentary Tract Surgery (1), Department of Clinical Radiology (2), Tampere University Hospital, Tampere, Finland; Hospital District Administration, Päijät-Häme Central Hospital (3), Lahti, Finland, Medical School, University of Tampere, Tampere, Finland (4).

Reprint requests: Antti Siiki, MD, PhD, Consultant in Gastrointestinal Surgery, Tampere University Hospital, Dept. of Gastroenterology and Alimentary Tract Surgery, Teiskontie 35, FIN-33521 Tampere, Finland.

If you would like to chat with an author of this article, you may contact Dr Siiki at antti.siiki@fimnet.fi.

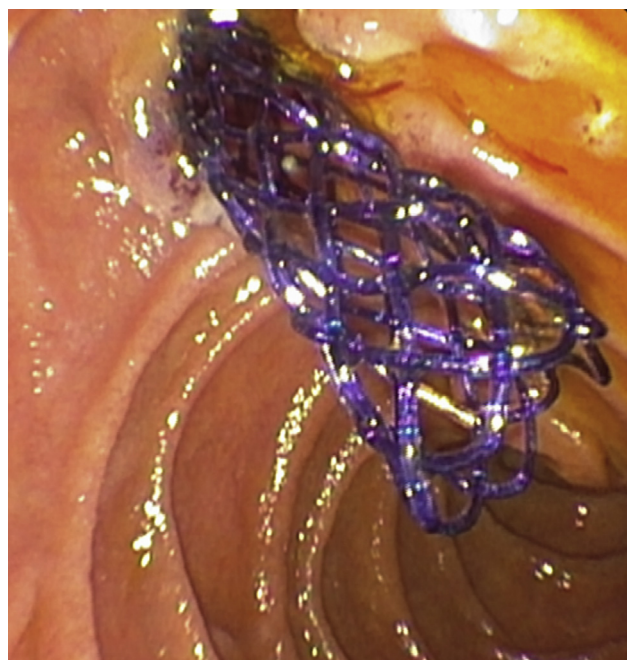


Figure 1. A braided 10-mm bore (60-mm length) self-expandable biodegradable poly-dioxanone biliary stent with golden radiopaque markers at both ends in situ as used in the study (Ella CS, Hradec Králové, Czech Republic). The stent was inserted across the papilla for treatment of post-cholecystectomy leak of the cystic duct.

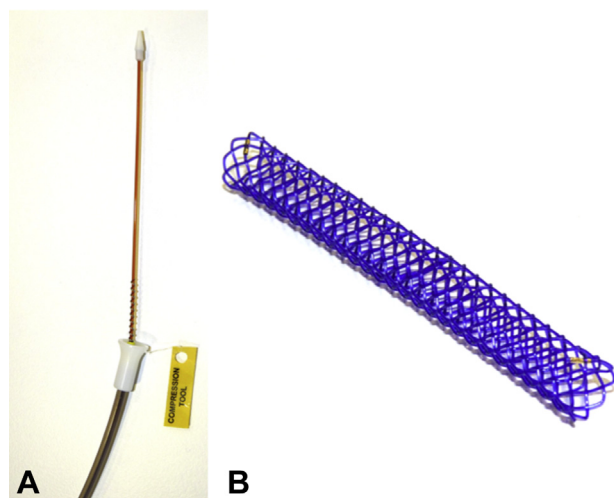


Figure 2. **A**, The endoscopic insertion device with a 10.5F shaft compatible with the working channel of a standard duodenoscope. **B**, A braided 8-mm bore (80-mm length) self-expandable poly-dioxanone stent before it is loaded into insertion device (Ella CS, Hradec Králové, Czech Republic).

with the novel insertion device further validated the technical success of insertion and short-term safety in endoscopic use.^{5,6} The aim of this study was to investigate the clinical feasibility and effectiveness of endoscopically inserted BDBSs in the treatment of postcholecystectomy cystic duct leak and benign biliary stricture (BBS) in long-term follow-up.

TABLE 1. Demographics and data on stent insertion in 13 patients treated with endoscopically inserted self-expandable biodegradable poly-dioxanone biliary stents

	Leak (n = 7)	Stricture (n = 6)
Median age, y (range)	73.0 (46-79)	62.5 (43-73)
Sex, women	1 (14)	4 (67)
Median bile duct diameter maximum (range)	9.0 (6-12)	13 (9-19)
Sphincterotomy performed	7 (100)	4 (67)
Stone or sludge extraction	2 (29)	2 (33)
Guidewire		
Standard .035	3 (43)	2 (33)
Stiff shaft .035	4 (57)	4 (67)
Stent length		
40 mm	5 (71)	1 (17)
60 mm	2 (29)	2 (33)
80 mm	0	3 (50)
Stent diameter		
8 mm	6 (86)	6 (100)
10 mm	1 (14)	0

Values are n (%), unless otherwise defined.

METHODS

Altogether, 13 patients with either postcholecystectomy cystic duct leak or BBS were prospectively recruited between 2014 and 2016 at Tampere University Hospital, Finland. Patients with surgically altered duodenal anatomy or considered noncompliant with follow-up protocol or incompatible with magnetic resonance imaging (MRI) were not recruited. The diagnosis of bile leak was based on clinical features, CT scan, and bilirubin content in drain output. In BBSs malignancy was excluded with CT and MRI scans, and at least 1 set of benign brush cytology samples was taken during earlier ERC and plastic stent insertion.

A standard duodenoscope (TJF-Q180V; Olympus, Hamburg, Germany) with carbon dioxide insufflation was used in ERC. The biliary duct was cannulated with a standard short guidewire and sphincterotome (Dreamtome RX44; Boston Scientific Corp., Marlborough, Mass). A braided self-expandable biodegradable poly-dioxanone 8- or 10-mm bore biliary stent with golden radiopaque markers at both ends (Ella CS, Hradec Králové, Czech Republic) was then inserted in the common bile duct across the papilla (Figs. 1 and 2). The insertion device (Fig. 2) with a 10.5F shaft, closely resembling the devices currently used in FCSEMSs, was introduced over a guidewire through the working channel of a duodenoscope. None of the strictures was dilated at the time of BDBS insertion.

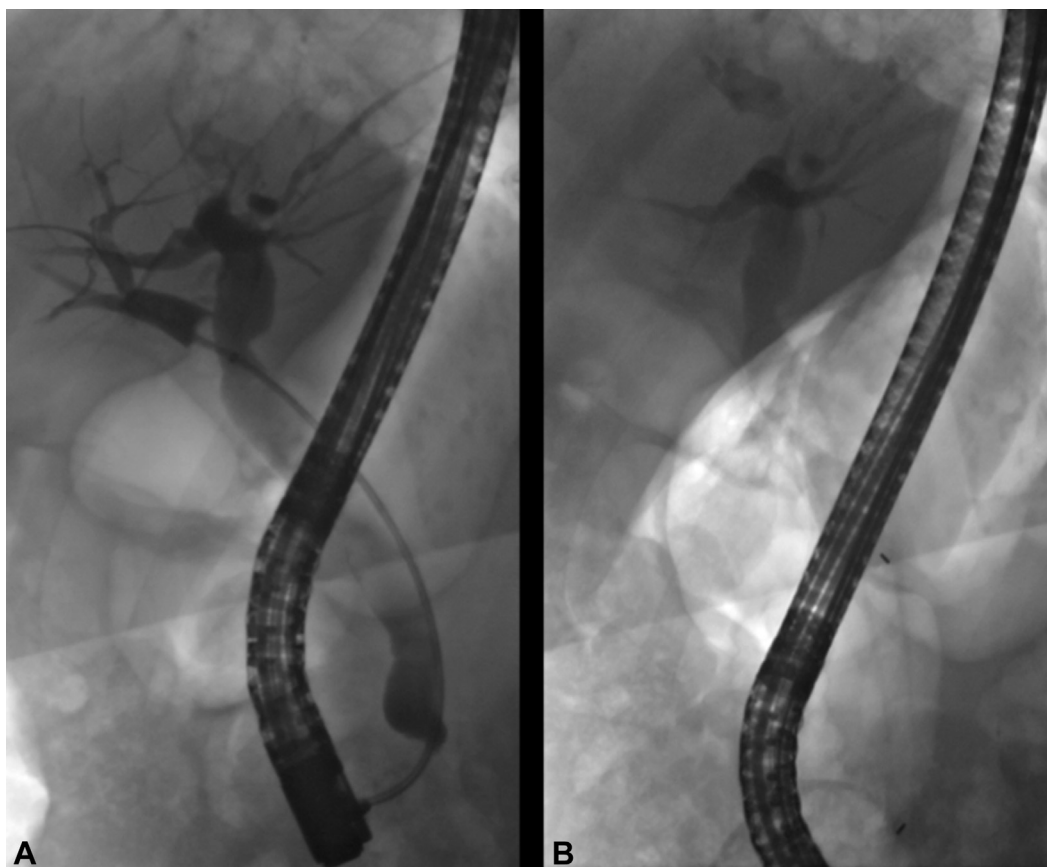


Figure 3. **A**, Endoscopic retrograde cholangiography image of a 71-year-old woman with a benign distal common bile duct biliary stricture, presumably secondary to earlier common bile duct stones. **B**, Fluoroscopy image after endoscopic insertion of a 40 × 8-mm self-expandable biodegradable biliary stent with radiopaque markers at both ends covering the stricture.

Both groups underwent a similar follow-up protocol: liver function tests at 1, 3, 9, and 12 months and MRI at 3, 6, and 12 months after BDBS insertion. Data on procedures, adverse events, and long-term results were prospectively recorded in the hospital database. At the end of follow-up the digital hospital record was reviewed for any unplanned admissions, changes in treatment strategy, or treatment failures. Median follow-up time was 21 months (range, 5-25.5). The primary outcome measure was clinical success rate of stent treatment, defined by absence of unscheduled interventions, change in treatment strategy, or stricture relapse during the follow-up time. Secondary outcome measures were technical success of endoscopic stent insertion, adverse events, or readmissions during the 30- and 90-day period after insertion as well as during the follow-up.

The Ethics Committee of Pirkanmaa Hospital District, Finland approved the study protocol. Informed consent was obtained from all patients for research use of BDBSs. The study was registered in [Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02353286) (NCT02353286) and was conducted according to the Helsinki Declaration. Statistical analysis was performed using SPSS Statistics version 22 (IBM Corp, Armonk, NY). Categorical variables were compared using the χ^2

or Fisher exact test and continuous variables using the Mann-Whitney U test. Statistical significance was set at $P < .05$.

RESULTS

Data on 13 patients treated with BDBSs for postcholecystectomy bile leak or BBS are presented in [Table 1](#). Endoscopic stent insertion was successful in all cases ([Figs. 1 and 3](#)). Data on clinical outcome, repeated MRIs, and liver function tests from both groups are presented in [Table 2](#). One patient was lost from follow-up in each group. In all patients during the first 30 days there were altogether 4 readmissions (31%), of which 2 were for pain after stent insertion, 1 (8%) for mild cholangitis, and 1 (8%) for mild post-ERC pancreatitis ([Table 3](#)). During the first 90 days there were 3 (23%) readmissions for mild cholangitis.

Postcholecystectomy bile leaks

In the leak group ERC with BDBS insertion was performed at a median of 4 days (range, 3-8) from laparoscopic cholecystectomy. All except 1 patient had a native

TABLE 2. Follow-up data with repeated liver function tests and magnetic resonance imaging

	Leak (n = 7)	Stricture (n = 6)
Median follow-up, mo (range)	21.0 (5-25)	21.5 (14-25)
Patients lost from follow-up	1 (14)	1 (17)
Treatment failure	0	1 (17)*
Liver function tests: normal values		
1 mo	7 (100)	6 (100)
3 mo	7 (100)	6 (100)
6 mo	6 (86)†	6 (100)
9 mo	6 (86)†	5 (83)†
12 mo	6 (86)†	5 (83)†
Magnetic resonance imaging		
3 mo	7 (100)	5 (83)
Stent in place	4 (57)	2 (33)
Stent not visible	2 (29)	1 (17)
Stent partially migrated	1 (14)	2 (33)
6 mo	6 (86)†	6 (100)
Stent in place	2 (29)	1 (17)
Stent not visible	4 (57)	5 (84)
12 mo	6 (86)†	5 (83)†
No stricture	6 (86)	5 (83)

Values are n (%), unless otherwise defined.

*Stricture relapse at 17 months after BDBS insertion.

†One patient in each group lost from follow-up.

papilla. One cannulation was performed with a double-guidewire technique with consequent insertion of a prophylactic pancreatic stent. The external drain was removed on median day 5 (range, 2-7) after stent insertion.

Endoscopic treatment was successful in all cases of post-cholecystectomy leak of the cystic duct (Table 2). Two patients (29%) had traces of stent still visible in MRI at 6 months (Table 2). One of these patients underwent ERC for pancreatic duct stent placement for chronic pancreatitis-related pancreatic duct stricture at 4 months, where BDBS remnants were removed with grasping forceps.

There were no 30-day ERC-related adverse events. One patient (14%) had mild cholangitis during the first 90 days. Additionally, 1 patient with severe comorbidities had an episode of severe lower limb ischemia and septic infection resulting in eventual multiorgan failure and death 4 months after BDBS insertion. This event was not considered to be ERC related (Table 3).

Benign biliary strictures

Two strictures (33%) were secondary to chronic pancreatitis. Others had distal common bile duct stricture of open etiology. However, no patients had postoperative stricture, sclerosing cholangitis, or autoimmune-associated disease.

TABLE 3. Details of adverse events and readmissions during the first 3 months

	Leak (n = 7)	Stricture (n = 6)
ERC-related adverse events 30 days	0	2 (33%)
Readmission 30 days		
Pain	0	2 (33%)
Acute cholangitis	0	1 (17%)
Post-ERC pancreatitis	0	1 (17%)
Other adverse events (not ERC related)*	1 (14%)	0
Readmission 90 days		
Acute cholangitis	1 (14%)	2 (33%)

ERC, Endoscopic retrograde cholangiography.

*See text.

Five patients (83%) had previous single plastic stents in place.

With biodegradable stents stricture treatment was successful in 83% (Table 2). In most patients (84%) the stents were not visible at the 6-month MRI (Fig. 4). There was 1 (17%) treatment failure during follow-up: the patient previously treated with an FCSEMS developed a stricture relapse at 17 months. In this case permanent treatment with an FCSEMS was chosen instead of operation because of unacceptable anesthesiology risk.

Two patients had mild ERC-related adverse events: 1 cholangitis (17%) and 1 post-ERC pancreatitis (17%). Additionally, 2 patients (33%) were readmitted overnight for pain after stent insertion (Table 3). During the first 90 days there were 2 readmissions for mild cholangitis (33%).

DISCUSSION

This pilot study evaluated the long-term clinical utility of endoscopically inserted BDBSs in postcholecystectomy bile leaks and BBSs. The biocompatibility and degradation profiles have been demonstrated in several studies.⁷⁻⁹ Furthermore, the largest study on BDBSs yielded an encouraging long-term success rate of 82% in the percutaneous management of refractory postoperative or chronic pancreatitis-related strictures.⁴ Our main result was that the endoscopic insertion of BDBSs was highly successful, and stents were not associated with an alarming rate of adverse events. Long-term follow-up of up to 2 years revealed no unexpected problems. Most importantly, the clinical efficacy of stricture management was excellent.

With the novel insertion device, stent placement was successful in all cases. As in the first case reports of endoscopic BDBS use,^{5,6} some stents had to be adjusted to the proper location with grasping forceps or extraction balloon. The factor limiting the endoscopic use of BDBSs has been the lack of a proper insertion device fitting into the working channel of a duodenoscope with controlled

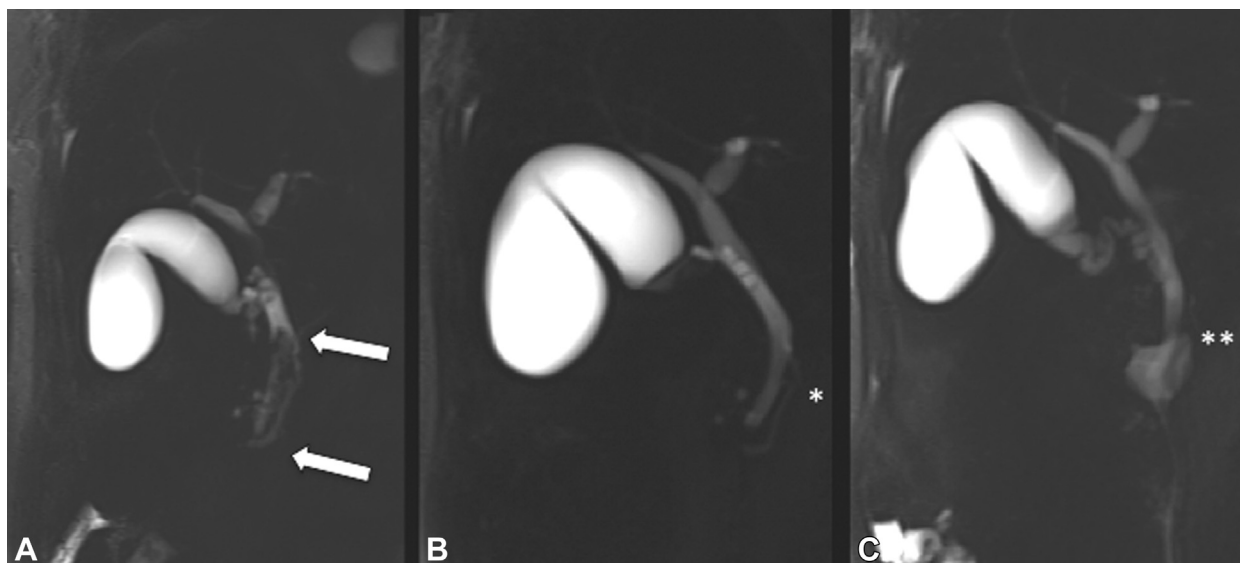


Figure 4. **A,** The biodegradable stent is visible as a filling defect of the common bile duct in coronal T2 haste thick slab magnetic resonance imaging at 3.5 months after stent insertion (*arrows*). **B,** At 6 months the stent has degraded and is not visible in a similar sequence (*star*). **C,** At the 12-month magnetic resonance imaging there are no signs of stricture relapse or secondary stent-associated changes. The common bile duct is blurry because of overlapping right renal pelvis (2 stars).

stent delivery and expansion in the bile duct. Further improved types of BDBSs resembling the current smooth insertion devices of FCSEMSs may well make insertion easier. Degradation of BDBSs, which usually taking between 3 and 6 months, was similar to that reported earlier.^{4,7,10} The radiologic appearance of the novel poly-dioxanone BDBSs in MRI has not been studied before (Fig. 3). In the present series neither radiologic visibility or invisibility nor signs of stent migration at the 3- or 6-month follow-up MRI seemed to correlate with clinical outcome. A previous study of the percutaneous use of BDBSs reported clinically significant migration in 2% of patients, suggesting that not all stent migrations necessarily result in treatment failure.⁴

There were no unexpected adverse events related to endoscopic use of BDBSs. The readmissions for abdominal pain were probably because of gradual stent expansion during the first days. Nearly one fourth of patients had a mild cholangitis during the 3 months after stent insertion. This may be because of slow degradation and defragmentation of the stent intermittently blocking bile flow and causing acute cholangitis. All episodes were self-limiting and managed with brief antibiotic treatment. Possibly characteristic of poly-dioxanone stent treatment, similar findings, and rates of 26% cholangitis have been reported earlier in series of percutaneous use of BDBSs.⁴ Although our study was underpowered to re-evaluate it, the occurrence of acute cholangitis has been associated with treatment failure of a stricture.⁴ Moreover, episodes of acute cholangitis are also associated with traditional plastic stents and FCSEMSs in up to 10% to 30% of cases.^{11,12}

In postcholecystectomy bile leak, the clinical success rate of BDBS treatment was expectedly outstanding. In a

simple postcholecystectomy cystic duct leak, as in all the current cases, conventional management with external drain followed by endoscopic sphincterotomy and insertion of a single plastic stent is usually unproblematic.¹³ In a single animal study comparing plastic stents and 8-mm bore BDBSs, the BDBS was associated with faster bile leak resolution, presumably because of a larger stent diameter and better downstream bile flow.¹⁴ When BDBSs are used, a second endoscopy to remove the plastic stent can be avoided, possibly balancing the inevitably higher cost of the stent.

In BBSs long-term success rate of BDBSs was over 80%. This is identical to the results of an earlier study, where stricture recurrence occurred in 18% of BBS patients when BDBSs were inserted percutaneously.⁴ Two thirds of our strictures were benign distal common bile duct stenoses that could probably have been successfully treated with FCSEMSs. The remaining third was secondary to chronic pancreatitis, often poorly resistant to any method of endoscopic treatment, except long-term FCSEMS use.¹⁵ The only treatment failure was in a patient whose previous treatment with FCSEMSs had failed because of stent migration. As with bile leaks, the main advantage of BDBSs over FCSEMSs in BBS could be the avoidance of stent removal. Contrary to silicone-covered FCSEMSs, biodegradable stents could also be used across the hilar region or cystic duct confluence. Furthermore, an accidentally long indwelling time, for example, because of poor patient compliance in alcohol-related chronic pancreatitis, could be avoided with BDBSs.

Our study supports the current view of the safety and good biocompatibility of biodegradable materials in human

biliary environment.^{2,3,7-9} Previously in the esophagus, poly-dioxanone stents have been associated with secondary epithelial hyperplasia and strictures.¹⁶ Such a potential hazard must also be borne in mind in future studies on BDBSs in the biliary duct. However, we perceived no adverse foreign body reaction leading to clinical consequences or MRI findings in our patients. This is in line with animal studies, where the tissue reaction of BDBSs is reportedly temporary and does not differ from epithelial reaction caused by plastic stents even in blinded histologic analysis.^{7,14} The only study comparing the reaction of biliary epithelium to BDBSs or FCSEMSs suggested that expression of proteins associated with tissue healing is different and potentially closer to intact bile duct after BDBS indwelling.¹⁷ In addition, the study by Mauri et al⁴ reported no secondary biodegradable stent-related strictures or hyperplasia in the long follow-up of 107 patients.

The strength of the study is the long follow-up time of nearly 2 years, during which recurrences or stent-related problems, such as secondary strictures because of epithelial hyperplasia, may appear. Additionally, the meticulous surveillance with repeated liver function tests and repeated MRIs during the first year after stent insertion was conducted to record in detail all radiologic and clinical treatment failures and adverse events. All our patients were from the catchment area of a single surgical emergency department, making us confident of capturing all readmissions or unscheduled visits. The small numbers of patients, the dropout rate, and absence of control groups with conventional treatment are the major weaknesses. Moreover, we used mostly 8-mm bore stents, whereas those with 10-mm bore apparently yield better clinical results in BBSs.⁴ Further product updates of the stent insertion device may overcome the challenges with the old-generation device we used. It may therefore be premature to draw firm conclusions on the clinical efficacy of BDBSs in endoscopic stricture management.

In summary, novel self-expanding poly-dioxanone BDBSs may be safely used even in ERC. The clinical feasibility and safety as well as long-term patency were confirmed in follow-up lasting up to 2 years. There were no unexpected adverse events. The surveillance with repeated MRI during the first year revealed the anticipated degradation pattern.

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